Journal of Medical and Biological Engineering
https://doi.org/10.1007/s40846-023-00810-2

REVIEW ARTICLE

Comparing Transcranial Direct Current Stimulation (tDCS) with Other Non-Invasive Brain Stimulation (NIBS) in the Treatment of Alzheimer's Disease: A Literature Review

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Received: 23 June 2023 / Accepted: 28 July 2023

Abstract

Purpose Identifying the effective treatments for diseases has been a critical issue in daily clinical practice, especially for Alzheimer's dementia (AD). Abundant evidence showed that non-invasive brain stimulation (NIBS) has the potential to slow or reverse cognitive function decline. Among them, the transcranial Direct Current Stimulation (tDCS) would be relatively safe for patients with AD. The purpose of this study was to review the relevant articles to explore the mechanism and effect of tDCS and other NIBS in AD treatment.

Methods All the reported works were retrieved from two databases (i.e., PubMed and Google Scholar) by using the keywords "NIBS" and "AD". The mechanisms and effects of different NIBS applied in AD, including transcranial ultrasound stimulation (TUS), transcranial near-infrared (tNIR) light therapy, transcranial magnetic stimulation (TMS), and transcranial electric stimulation (TES) were reviewed.

Results The positive effects of TUS and tNIR on AD were supported by a few small samples and uncontrolled pilot studies. tDCS and repetitive TMS have been often used in an attempt to improve the cognition in people with brain disorders. Both the tDCS and TMS have benefits in AD by introducing long-term potentiation like change in synaptic strength. The reports showed that tDCS could be more safe, convenient, affordable, and well-tolerated method among all applications for AD treatment.

Conclusion In this review, it was shown that all the NIBS have positive effects on AD treatment. But, however, tDCS showed the great potential in improving the cognition of AD.

Keywords Alzheimer's dementia · Non-invasive brain stimulation · Transcranial direct current stimulation

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Published online: 23 August 2023

1 Introduction

1.1 Needs for the Therapeutic Strategies of AD

Alzheimer's disease (AD) is the most common type of dementia including 60%–80% of all dementia cases [1]. However, the current medications for AD are either limited to efficacies in the progression of AD or complicated with serious side effects [2–5]. AD is generally considered to be associated with the amyloid cascade hypothesis which can initiate the downstream brain atrophy and cognitive decline [6–8]. Recently the US Food and Drug Administration (FDA) approved the uses of both Aducanumab and Lecanemab, were monoclonal IgG1 antibodies targeting the aggregated forms of amyloid β (Aβ) [9]. However, there is no persuasive evidence to support the approval of aducanumab as the validity from the studies is uncertain [10, 11]. It was studied that these two drugs could lower the brain Aβ burden but could cause the most common side effect, amyloid-related imaging abnormality (ARIA), which includes brain edema and hemorrhage. [12]. The ARIA might also lead to new signs and symptoms including headache, worsening confusion, dizziness, visual disturbances, nausea, and seizures [12]. However, it requires to find the alternative or complementary therapeutic strategies for AD due the controversies of drug therapy for AD.

1.2 Transcranial Direct Current Stimulation (tDCS) and Other Non-invasive Brain Stimulation (NIBS) in AD

The hypothesis of pathogenesis of AD is that the abnormal Aβ plaque deposition and hyperphosphorylation of intra-neuronal tau protein lead to mitochondrial dysfunction, inflammatory damage, synaptic failure, depletion of neurotrophin, deficit of neurotransmitters, vascular injury, and neuronal loss [6–8]. The synaptic dysfunction of AD contributed by the Aβ oligomers would induce excess calcium entry into the neurons via N-methyl-D-aspartate receptors (NMDARs) [13]. Consequently, the synaptic plasticity regulation mechanisms such as metaplasticity are altered before the loss of synapse. Long-term potentiation (*LTP*) and Long-term potentiation (*LTD*) are two main forms of synaptic plasticity which are involved in learning and memory [14]. The soluble oligomers of Aβ would induce a significant reduction of LTP by facilitating LTD induction [15]. Thus, the conditions that promote LTD, i.e., following excessive Aβ load in the early-onset forms of the disease, can lead to loss of synapses. Additionally,, the promoting LTP can represent a protective mechanism in order to preserve the synaptic plasticity and brain connectivity [16].

NIBS refers to those techniques that act on brain physiology without the need for surgical procedures involving the electrode implantation, such as deep brain stimulation, direct cortical stimulation, or epidural stimulation techniques [17]. It can be used to decrease the inflammation, increase the cerebral blood flow, modulate the activity of neurotrophic factors or neural excitability, and enhance the cortical function by facilitating LTP or reducing LTD, and thus would offer a potential means to slow or reverse the cognitive decline [18–22]. Numerous evidences support the use of NIBS techniques as tools for enhancing the cognitive function in healthy subjects and as therapeutic agents for patients with neurocognitive disorder [23–25].

According to the power sources, the techniques of NIBS include transcranial ultrasound stimulation (TUS), transcranial near-infrared (tNIR) light therapy, transcranial magnetic stimulation (TMS), and transcranial electric stimulation (TES) (Fig. 1). tDCS is a common type of TES. It is a simple, safe, convenient, affordable, and well-tolerated method that has been tested to modify the cognition of healthy participants and mitigate the cognitive symptoms in AD for two decades. [21, 26–28]. The tDCS and repetitive TMS (rTMS)-induced cognitive enhancement have been studied much more than the same effects produced by TUS and tNIR. [17].

The aim of this study was to systematically review the related articles to explore the effect of tDCS and other non-invasive brain stimulation (NIBS) in AD. The characteristics and mechanisms of each NIBS device applied to AD were discussed.

2 NIBS Techniques in AD

2.1 Transcranial Ultrasound Stimulation (TUS) in AD

Ultrasound is a mechanical wave with a frequency above the human hearing range, from 20 kHz to 1 GHz. It travels with alternating compression and rarefaction, by transmitting energy through molecular movements. The high-intensity ultrasounds use ultrasound intensities > 3W/cm2 and low-intensity ultrasounds (LIU) with < 3W/cm2 [29]. High-intensity focused ultrasound is used to cause the significant tissue heating for therapeutic ablations, whereas LIU produces mechanical effects on tissues that do not cause the heating or damage. Beyond direct effects on electrical activity, LIU has been shown to modulate the activity of neurotrophic factors that could produce the secondary effects on neural activity and plasticity [18]. In TUS stimulation, the transcranial focused ultrasound (tFUS) transmits LIU into the brain non-invasively and focuses on deep brain regions [30].

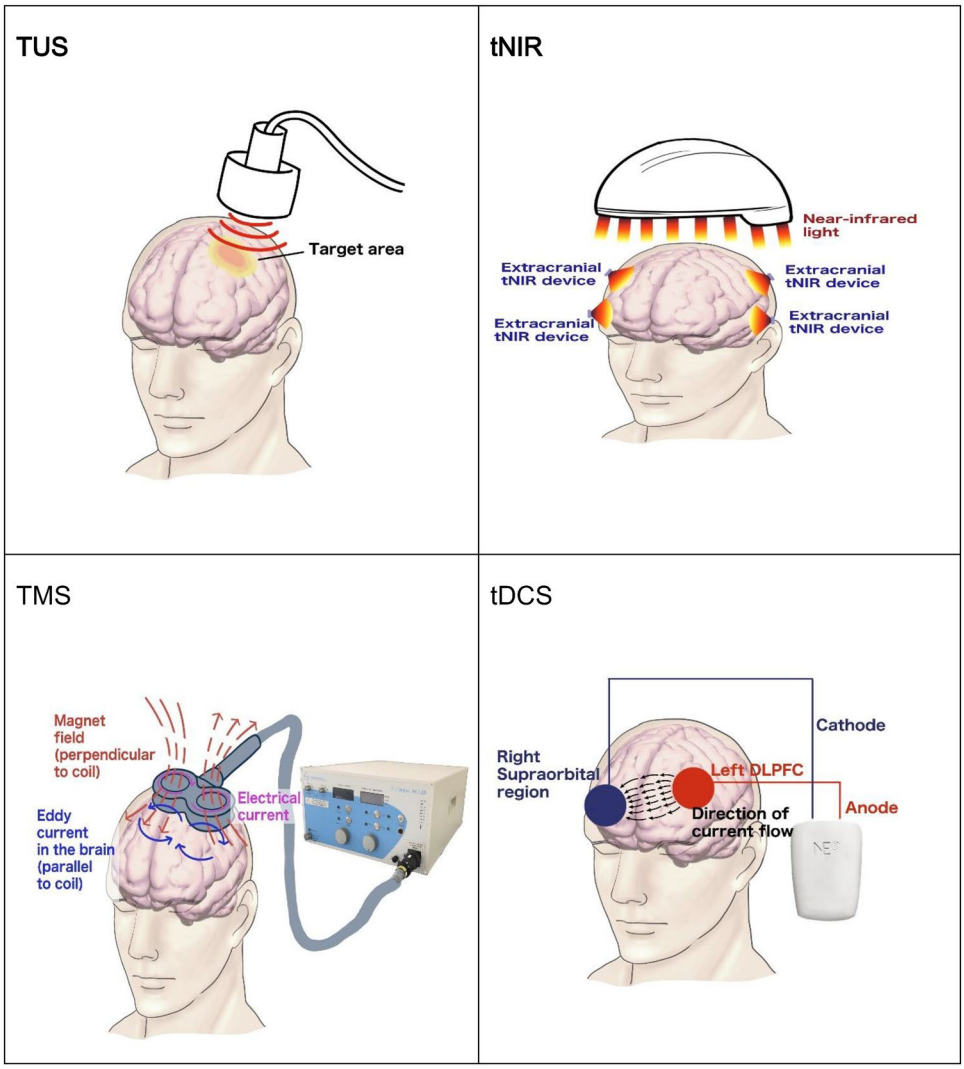

Fig. 1 The schematic diagram of each non-invasive brain stimulation. TUS: transcranial ultrasound stimulation; tNIR: transcranial near-infrared light therapy; TMS: transcranial magnetic stimulation; tDCS: transcranial Direct Current Stimulation. DLPFC: dorsolateral prefrontal cortex

TUS stimulation treatment of various durations was associated with different beneficial effects against Aβ and tau-induced toxicity and structural damage in the brains of AD transgenic mouse models [31–33]. TUS has provided some solid evidence for its beneficial effects on brain plasticity and function as well as neuronal circuit integrity in experimental animal studies [31]. However, no clinical evidence has been provided on the mitigation of neurotoxicity after ultrasound treatment in humans [31]. At the clinical level, three studies have reported the alterations in brain networks after ultrasound therapy in AD patients [34–36]. These three pilot studies were performed with quite small patients and in an uncontrolled design.

2.2 Transcranial Near-Infrared (tNIR) Light Therapy in AD

Low-power tNIR light-emitting diodes illuminate the light that is outside of the visible spectrum of human eyes but can efficiently penetrate the scalp, skull, and meninges to reach the brain parenchyma [37, 38]. It was proposed that mitochondrial dysfunction, inadequate supplies of adenosine triphosphate (ATP), and oxidative stress were contributory factors in AD [39]. This near-infrared photon absorption by cytochrome C oxidase might dissociate the inhibitory nitric oxide, unit IV of the mitochondrial respiratory chain, and thereby allowing the respiration to resume to be unhindered and to increase the ATP synthesis. The tNIR light could prove valuable for AD therapeutics by targeting the mitochondria, increasing ATP in proteasomes for ubiquitination of misfolded proteins, decreasing inflammation and even antibacterial and anti-viral effects [40–43].

So far, there has been a limited number of clinical trials that have used tNIR to treat the patients with AD. Two pilot studies demonstrated the safety and positive cognitive improvements in small sample size of patients with dementia [44, 45]. Very small sample or fuzzy number of AD in these

two studies made no clear evidence of efficacy in cognition of AD.

2.3 Transcranial Magnetic Stimulation (TMS) in AD

TMS is a stimulation method in which a changing magnetic field is used to cause the electric current that can modulate the neuronal activity in an area of interest in the brain, with a powerful, rapidly fluctuating, handheld electromagnet [46]. These currents cause direct axonal excitation or transsynaptic activation of neurons, depending on the excitability properties of the neural structure and their orientation in the magnetic field-induced electric field. It pulses at a specified frequency and intensity, and the repetitive TMS (rTMS), can induce changes in brain excitability that can persist for some time after the period of stimulation [47].

Both high- and low-frequency rTMS significantly modulated the widespread brain activity [48]. The LTP induced by high-frequency magnetic stimulation (100 Hz), and related synaptic enhancement have been reported in animal studies following 10 and 20 Hz magnetic stimulation [22, 49, 50]. This, strongly support the potential mechanisms of rTMS benefits in AD by LTP -like changes in synaptic strength. After low-frequency magnetic stimulation, the GABAergic synthesizing enzymes and transporters increase, as well, after high-frequency stimulation, the number of immunocytochemically identified inhibitory cells decreases [51–53]. With respect to the clinical effects of stimulation, low-frequency rTMS protocols were known to result into the cortical suppression and inhibition, whereas the high-frequency stimulation would increase the cortical facilitation and excitability [51–54].

In AD, several small pilot studies have shown promising results by using rTMS protocols to improve the global cognition or language function [55–57]. A recent meta-analysis supported the beneficial effect of rTMS on cognitive functions in patients with AD [58]. A similar result was reported by a study with eight articles focusing on rTMS treatment of AD and suggested the potentiality for the improvement in cognitive measures after rTMS treatments. But, the results did not clearly show whether rTMS was significantly more effective than sham [59].

2.4 Transcranial Electric Stimulation (TES) in AD

TES is the way that two or more electrodes are applied to a person's scalp, by using electrical currents to penetrate the scalp and pass through the brain cortex to alter the brain function [60]. The Polarizing effects evoked by the electric fields (EFs) can be categorized as (1) "suprathreshold" stimulation—directly triggering the neuronal action potentials; (2) "subthreshold" stimulation—primarily exert modulatory effects on ongoing neuronal activity and excitability [17, 61]. In the electrical NIBS techniques, the group of suprathreshold stimulation (that primarily induce the activity of neurons) includes high-intensity short-pulse TES, electroconvulsive therapy (ECT), and electro-anesthesia. The group of subthreshold stimulation includes the forms of low-intensity (e.g., few mA) and sustained (e.g., minutes) TES, such as transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS), and tDCS [17, 62]. The suprathreshold techniques ultimately affect the behavior by modulation of endogenous networks, whereas the subthreshold techniques can influence the firing in the active system [63, 64]. The electric field intensities produced in the brain by suprathreshold techniques are often two orders of magnitude above the subthreshold, allowing for the triggering of action potentials [17]. It is a reasonable inference that adverse effects are less in subthreshold than that of in suprathreshold electrical stimulation.

In the suprathreshold technique, high-intensity short-pulse TES, electro-anesthesia, and ECT were not investigated for the therapeutic application of AD because of side effects, such as seizure, cardiac arrhythmia, hemodynamic changes, or impaired cognitive function [65–69].

In the subthreshold electrical technique, three different waveforms of the currents are applied to induce the EF: (1) tDCS: the applied current is constant over time; (2) tACS: the current is rapidly alternated at a specific frequency (1–45 Hz), in a sinusoidal wave, to entrain cortical oscillations; and (3) tRNS: a whit-noise band-limited waveform (frequent spectrum 0.6–640 Hz) with full-band current spectrum is applied to boost the endogenous rhythms by means of stochastic resonance. [70, 71] (Fig. 2). The depolarization or hyperpolarization is below the spike threshold. They do not induce the massive synchronized discharge of action potentials as TMS do. They all share the same approach with respect to the electrode montage and in all cases, the duration of stimulation is typically 10–30 min with a peak current of 1–2 mA [72].

The applied tACS current altering the transmembrane potential of neurons entrains the neuronal firing from a large number of underlying neurons to the exogenous frequency but did not alter the neuronal excitability [73]. In general, the synchronous oscillations of high frequency, such as the gamma band of electroencephalography, represent a highly organized form of brain activity. tACS is an appealing approach with the evidence of abnormal brain oscillations in AD [74]. Alteration in spontaneous oscillatory activity can be accomplished with tACS, which in the main frequency bands of physiological brain activity does not induce the plasticity [75].

The tRNS is a subtype of tACS that involves the application of random noise oscillations above selected brain regions to modulate the cortical plasticity. It can induce the mechanisms of temporal summation of neural activity due to

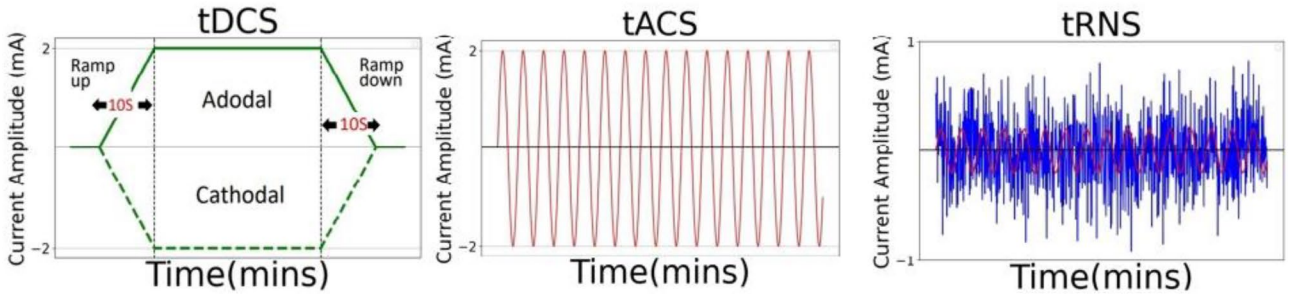

Fig. 2 This schematic diagram illustrates different subthreshold TES waveforms. Left: The tDCS waveform displays both the anodal (green) and cathodal (dash green) electrodes, which must remain active simultaneously throughout the stimulation process. The current is ramped up (10 s) to the desired current intensity and when said intensity is reached the current intensity is held at that level for the duration of stimulation. The ramped off is also 10 s usually. Middle: The tACS waveform illustrates the characteristic pattern of oscillatory current delivery between the electrodes. Right: tRNS is similar to tACS in using alternating current. The tRNS waveform demonstrates the application of generalized random noise current intensity during the stimulation process

the reason that the time constant of a neuron is long enough to allow the sum of two or more stimuli in a close temporal sequence [76]. The effects of tRNS were also explained by the increase of neuronal excitability via stochastic resonance. Whereas the weak neural signal detection in the central nervous system was enhanced when noise was added [77]. Although there have not been any published reports investigating the potential therapeutic benefit of tRNS in AD, it has been shown to improve the fluid intelligence in healthy adults when paired with adaptive cognitive training [78]. A study proposed that the usage of tACS allowed modulating the brain oscillations and in turn influences the cognitive processes, by demonstrating the causal link between the two [79]. However, there has little evidence been collected with respect to tACS in addressing the gamma oscillatory activity in AD based on evidence from animal models, whereas no study has so far employed tRNS in AD [80, 81].

2.5 tDCS in AD

2.5.1 Neurophysiological Mechanism of tDCS

To date, the majority of studies on subthreshold electrical techniques in AD have been conducted by using tDCS. At the neuronal level, the primary neurophysiological mechanism of tDCS action of the cerebral cortex is assumed based on modulating spontaneous neuronal network activity through polarization of the resting membrane potential [27, 82, 83]. As the weak current of tDCS flows inward the brain, it depolarizes the soma, or cell body of neurons near the anodal electrode by bringing them closer to their thresholds for firing an action potential, whereas the ionic gradients near the cathode have the opposite effect [84–86]. The induced extracellular voltages are not uniform across the neurons but changed depending on the cellular compartment [87, 88]. The weak EFs perpendicular to the main orientation of neurons do not polarize the somatic membrane significantly but may still influence the functions [89]. Membrane potential at the soma is linear with EF intensity along the primary neural axis for weak, subthreshold EFs [88]. The effect on membrane polarization affects potentially every aspect of neuronal, electrical, and synaptic activity. The changes in neuronal excitability are reflected in both spontaneous firing rates and responsiveness to afferent synaptic inputs [89–91]. Furthermore, the increased excitability of local neurons by anodal stimulation is assumed to increase the blood flow around the stimulation site, and induce subsequent metabolic changes among neurons [92].

The other physiological mechanism of tDCS in the changes of the low-frequency long-range network connectivity patterns observed as resting state networks are reflected in modulation of local, higher-frequency activity, particularly in the gamma frequency band [93]. The decrease in local GABA by tDCS and increase in firing rates lead to an increase in local gamma-band oscillatory activity, which will lead to an increase in functional connectivity in highly connected regions [94]. tDCS leads to an increase in gamma activity has been supported by the study of magnetoencephalography [95].

2.5.2 Biochemical Mechanism of tDCS

In biochemical mechanism of tDCS on neural circuits, EF of tDCS modifies the variety of neurotransmitter systems in synaptic microenvironment. The anodal tDCS may enhance the excitatory synaptic transmissions by changing the balance between glutamate and GABA activities, with enhancing the effect on glutamatergic neurons by reducing GABA activity [94, 96–102]. In the tDCS induced membrane depolarizing or hyperpolarizing effects on glutamatergic synapses, tDCS enhances or reduces calcium influx via NMDARs and voltage-gated calcium channels. The enzyme

cascades are active as the alteration of intra-neuronal calcium. These insert glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor) into or remove them from the subsynaptic membrane, by strengthening or weakening the synaptic connections [94]. The amount of intracellular calcium controls the induction of both LTP and LTD, if excitability-enhancing LTP or excitability-diminishing LTD takes place. Anodal tDCS presumably induces high calcium concentration which will result into LTP, whereas cathodal tDCS induces low calcium concentration, which will result into LTD. tDCS induces long-term neuromodulation.

The other contributing factors to the neuromodulatory action include changes in brain-derived neurotrophic factor (BDNF) expression. The tropomyosin-receptor kinase (Trk) receptors, a family of growth factor receptors, may also be attracted to the synapse in anodal tDCS [103]. The presence of calcium ion influx increases the release of BDNF into the synaptic cleft [104]. Postsynaptic Trk receptor induces later phase LTP and favors the opening of NMDA receptors, which also promotes later phase LTP, whereas the opposite is involved in cathodal tDCS, promoting the later phase LTD [105, 106].

The effects of tDCS may also involve other factors and the regulation of various neurotransmitters, such as GABA, dopamine, acetylcholine, serotonin, adrenaline and noradrenaline [96, 99, 107–110]. These neural events are considered to improve the psychiatric symptoms and the cognitive function [83, 111].

Human studies proved the benefit of tDCS on cognitive function in AD [28, 112, 113]. However, there were inconsistent results suggesting that the tDCS showed no significant effect on the performance of the face-name association task or verbal memory function [114, 115]. Nevertheless, the review of the past 18 research reports and the meta-analysis results of tDCS on AD cognitive function still hold the conclusion that tDCS has a positive effect [113, 116].

In summary, the mechanism and benefits of all current studies on AD with various NIBS are shown in Table 1.

3 Discussion

3.1 Benefits and Limitations of TUS, tNIR, and tACS

Although the predominance of small, heterogeneous, proof-of-principle studies precludes definitive conclusions from past studies, NIBS remains an active area of investigation for the treatment of AD and may play a useful role in future multimodality treatment approaches that are likely to be required in AD [59]. tFUS applies acoustic energy to highly specific intracranial areas, including both cortical and deep brain regions, with good spatial specificity and significant

Table 1 Mechanism and effects of Non-invasive brain stimulation in AD

Type	Primary mechanism on cognition	Effects	Side effects and limitation
TUS	Low-intensity ultrasound modulate the activity of neurotrophic factor	Increase of brain connectivity, regional cerebral metabolic rate of glucose Modulating brain active and cognition (by three small pilot studies, uncontrolled designs)	Potential thermal and damaging effects by high frequency
tNIR	Near-infrared photon absorption by cytochrome C oxidase →dissociate inhibit nitric oxide →ATP synthesis increasing →decreasing inflammation	Improvement of cognition (by two small pilot studies)	Safe, no side effect But little evidence to direct neural activity
TMS	High-frequency rTMS induces LTP and increases cortical facilitation and excitability, whereas low-frequency rTMS resut in cortical suppression and inhibition	Improve language, attention, memory, executive performance or global cognitive function (by meta-analysis including 13 studies and review articles which includes 11 studies)	Side effects with seizure, syncope, headache, pain, vomiting and even emotional change Limitation: most limited on DLPFC, fails to demonstrate a clinically meaningful TMS benefit in AD
tACS	tACS current alters the spontaneous oscillatory activity of brain activity	No suggestion yet	No suggestions yet
tRNS	Increase the neuronal excitability via stochastic resonance	No published report in human AD yet	No suggestions yet
tDCS	Anodal stimulation increases excitability of focal neuron, Ca^{2+} influx increasing→ induce LTP; Cathadal tDCS induces low calcium concentration →result in LTD	Positive effect or negative efficacy is under debate by the review study that including past 10 studies; and positive effect supported by the meta-analysis which includes 7 past studies	Little side effect-fatigue, itching, headache, nausea, insomnia Evidence still in debate

depth penetration [36]. It may have the potential to serve as a novel NIBS tool for the treatment of AD. It can be suggested that for clinical TUS brain stimulation, the current techniques and certified systems (such as the pulse frequency, the delivery mode, and the ultrasonic energy) have to be developed and further studies are required to understand its therapeutic mechanism, safety, and efficacy [36].

tNIR light therapy is a relatively new approach to photobiomodulation for treating brain disorders and possibly for enhancing the cognitive function in dementia [117]. There are only few evidences to date for the tNIR producing the direct neural activity and there have not been any studies that have shown that tNIR induces LTP or LTD in ex vivo brain slices [17].

A recent FDA review for approval of a commercial TMS system for the treatment of AD suggested that current evidence fails to demonstrate a clinically meaningful TMS benefit in AD [51]. One of the limitations of TMS for AD treatment is that the insufficient number of patients are included in those studies. The other is that most of these studies have stimulated the brain regions on the DLPFC, and therefore, the non-significant rTMS effects of other brain regions should be interpreted with caution. Also, the effective treatment of rTMS for AD still needs to be developed.

There are two issues that have questioned the effect of tACS on cognition. First is whether the brain oscillations reflect a fundamental mechanism in cortical information processing or just an epiphenomenon is still unresolved [79]. The second is the simultaneous measurement of EEG, magnetic (magnetoencephalographic), or imaging (blood-oxygen-level dependent) signals during tACS was not feasible due to strong artifacts [118]. The retinal phosphene perception during tACS in a wide frequency range (6–70 Hz) is a side effect of specifically tACS [119].

3.2 Comparison of TMS and tDCS

TMS and tDCS have been often used in an attempt to improve the cognition in people with brain disorders. However, a major limitation across TMS and tDCS studies lies in the difficulty of comparing their efficacy due to the high variability observed across the study protocols [59, 120]. On the study protocol, tDCS has the advantage of being easier to use in double-blind or sham-controlled studies and easier to apply concurrently with behavioral tasks. In comparison with rTMS, tDCS is a low-cost technique, with portability and potential for home application, easy application, and practically fewer adverse effect. The human trials showed that the use of conventional tDCS protocols in human trials (≤ 40 min, ≤ 4 mA, ≤ 7.2 Coulombs) has not produced any reports of a serious adverse effect or irreversible injury [121]. However, current rTMS are not designed for at-home use. The TMS devices are always large, heavy and usually set up on a cart. Their size can be as a large microwave or mini fridge. Unlike tDCS, the head position needs to be fixed as rTMS is ongoing. This is hard for those with dementia with BPSD. In general, low-intensity electrical stimulation such as tDCS, is to induce non-painful (pre-pain) sensations. In contrast, rTMS may produce twitching in the scalp, temporary tinnitus, dizziness, or scalp pain. These may subside almost immediately after a session has been completed. The most serious side effect of rTMS is the potential for seizures, though the risk of TMS-related seizures is $< 1\%$ overall [122]. The comparisons of tDCS and rTMS are listed in Table 2.

Table 2 Comparison of tDCS and rTMS

Type	tDCS	rTMS
Positional accuracy	Placed directly on top of the desired stimulation area	Large size of the magnetic coils, quite difficult in targeting very specific areas
Target regions	Be used in targeting deeper regions of the brain is desired	Penetrate a few centimeters into the outer cortex, 1.5 to 3 cm below the scalp
Convenience	Allow to move	Undesired movement
Setting	be used in research settings, with guidance from a technician, or even at home by the individual themselves	limited within clinical setting It is not recommended for rTMS if if there are metal implants (electronic ear, pacemaker, etc.)
Action	Membrane potential modification	Actional potential generation
	Anodal tDCS induced excitatory effect; Cathodal tDCS induced inhibitory effects	High-frequency induced excitatory effect; Low frequency induced inhibitory effects
Side effects	Little side effects: tingling sensation, itching	S.E.:seizure, syncope, headache, scalp pain (most) at the stimulation side, nausea, vomiting, persistent twitching, temporary tinnitus, dizziness

3.3 tDCS- An Affordable Intervention Tool for AD

The positive or negative efficacy of tDCS on AD is under debate from the past studies, review, and meta-analysis research, respectively [23, 28, 112, 114, 115, 123–127]. The conflict results may be due to the reason that these studies reporting the data from case studies or small samples and there is a very different evaluation criteria, number and length of stimulation sessions, intensity and type of stimulation, target area, and type of sham stimulation between various studies. The results of tDCS in AD to date should be considered preliminary and further investigations are still required for detailed analysis. Also, further research is needed to explore under what circumstances the tDCS may be beneficial in AD [23].

Animal studies showed that the tDCS effectively improved the cognition, spatial learning and memory performance, alleviated Aβ burden and had a protective effect on neurons [128, 129]. The direct current stimulation in animal studies revealed that the long-lasting effects are protein synthesis-dependent and accompanied by modifications of intracellular cAMP [27]. It can modulate the cortical function by inducing the long-term after-effects on cortical excitability and neuronal plasticity [27, 130]. This brings about facilitatory or inhibitory effects, by broadly mirroring the workings of LTP and LTD [20, 21]. Studies showed that tDCS can modulate focally the rCBF and can be used to increase the oxygen availability or to facilitate the elimination of "neurotoxic" substances in degenerative disorders [92]. tDCS is assumed to be the reasonable therapeutic instruments since it alters (i) neuronal activity and (ii) human CBF, (iii) it has synaptic and non-synaptic after-effects (iv), it can modify neurotransmitters polarity-dependently, (v) it can alter oscillatory brain activity and the functional connectivity patterns in the brain [131]. In overall the possible mechanism of tDCS effect on AD is as shown in Fig. 3. tDCS modulates the synaptic environment and calcium reflux, influences the protein synthesis and BDNF release, modulates the LTP and LTD, and subsequently influences the regional cerebral blood flow and functional connectivity. These may play a major role for improving the declined cognition that induced by the misfolding and aggression of toxic Aβ. Thus, tDCS is a selectable tool for studying the effects of cognitive function in AD.

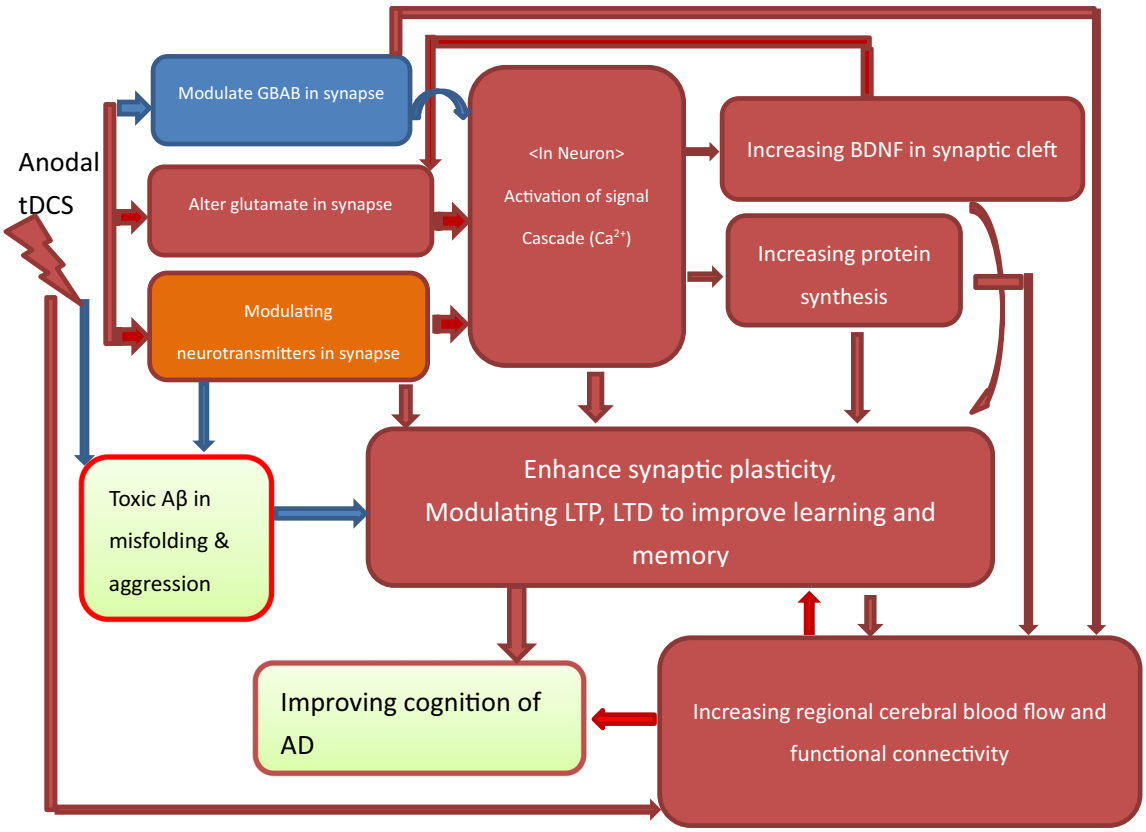

Fig. 3 Schematic diagram of possible mechanism of tDCS on improving cognition of AD. red color-induce or enhance; blue color: reduce or inhibit

4 Conclusion

All the NIBS methods witnessed the potential to be applied in the treatment of AD. Then, it is suggested that the tDCS can be used as a therapeutic instrument in AD since it causes changes in neuronal activity, blood flow to the brain, osmotic brain activity, communicative patterns of the brain, synaptic and non-synaptic effects, and neural modulation in AD.

Acknowledgements The authors wish to thank Prof. Kang-Ping Lin, Prof. Dong-Her Shih, Prof. Chou-Ching Lin and Dr. Min-Wei Huang for reviewing this paper. We thank I-Chun Hung, Hsiu Hua Wang, Liang Chao Huang and Li-Hui Wang for their excellent technical assistance extended for this study. We also thank Munusamy Thirumavalavan for his correction of English syntax errors.

Author Contributions Development of research ideas and design: CSMW and KSC. Data extraction: CSMW and WHC. Drafting of the manuscript: CSMW, KSC, YKY and KSC. All authors contributed to the development of the manuscript and approved the final version.

Funding The study was supported by research grants from Ministry of Science and Technology and Tainan hospital, Ministry of Health and Welfare, Taiwan.

Data Availability Not applicable.

Declarations

Competing interests The authors declare that they have no conflict of interest.

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

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